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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,841	06/27/2005	Jeremy S Lee	14859NP	6271
293 7590 04/28/2009 Ralph A. Dowell of DOWELL & DOWELL P.C. 2111 Eisenhower Ave Suite 406 Alexandria, VA 22314			EXAMINER BHAT, NARAYAN KAMESHWAR	
			ART UNIT 1634	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/511,841

**Applicant(s)**

LEE ET AL.

**Examiner**

NARAYAN K. BHAT

**Art Unit**

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 09 March 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) 14 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SE/US)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

## **DETAILED ACTION**

### ***Continued Examination under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on March 9, 2009 has been entered.

### ***Status of the Claims***

2. This action is in response to papers filed on March 9, 2009.
3. The previous rejections under 35 USC § 103 (a) not reiterated below have been withdrawn. Applicant's arguments filed on March 9, 2009 have been fully considered and are addressed following the rejection.
4. Claims 1-14 are pending in this application.
5. Claim 14 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention in the reply filed on September 20, 2007 and made final in the office action mailed November 2, 2007.
6. Claims 1-13 are under examination.

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3 and 5-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branton et al (USPN 6,627,067) in view of Granot et al (Biopolymers, 1982, 21, 873-883) and further in view of Aich et al (WO 99/31115, published June 24, 1999).

Regarding claim 1, Branton et al teaches a process of recording sequence information in a nucleic acid polymer comprising following step.

Regarding step 'a', Branton et al teaches modulating the translocation of the first poly dA nucleic acid strand and the second poly dT nucleic acid strand through a

channel between two media by applying voltage gradient across the channel (column 20, lines 37-67). The voltage gradient is one of the preferred methods to translocate nucleic acid as defined in the instant specification (USPGPUB, paragraph 0037).

Branton et al also teaches that the medium above the channel comprises poly dA strand and poly dT strand without forming the double stranded DNA at a lower voltage gradient (column 20, lines 57-58), thus teaching the medium above the channel is the dissociation medium. Branton et al further teaches that by applying higher voltage gradient across the channel allows the duplex to be formed at the channel and to translocate through the channel (column 20, lines 40-41), thus teaching the medium in the channel as the hybridization medium. Teachings of Branton et al of applying voltage gradient to modulate the translocation of duplex DNA through the channel is reasonably interpreted as modulating the electrostatic potential across the channel to modulate the duplex formation in the channel because voltage gradient maintains the negative and positive potential across the channel. Branton et al also teaches that nucleic acids are negatively charged (column 1, lines 55-56) and inherently attracts the positively charged metal ions. Branton et al do not teach explicitly the incorporation of metal ions in a nucleic acid duplex so that metal ion is permitted to enter the duplex for forming a metal containing base pair and if a metal ion is excluded from the duplex, a non-metal containing base pair is formed.

Regarding step 'b', Branton et al teaches that the channel separating the hybridization medium and the dissociation medium is dimensioned to allow linear translocation of the nucleic acid duplex (column 20, lines 41-43).

Regarding step 'c', Branton et al teaches that the single stranded poly dA oligonucleotides hybridizes to complementary poly dT oligonucleotides to form a duplex (column 20, line 40), which encompasses the first and the second nucleic acid strands comprise a plurality of nitrogen-containing aromatic adenosine purine bases covalently linked by a backbone, the nitrogen-containing aromatic bases of the first nucleic acid strand being capable of being joined by hydrogen bonding in the hybridization medium to the nitrogen-containing aromatic thymine bases of the second nucleic acid strand so that the nitrogen-containing aromatic bases on the first and the second nucleic acid strands form hydrogen-bonded base pairs in stacked arrangement in the nucleic acid duplex. Branton et al are silent about hydrogen-bonded base pairs being capable of interchelating the metal cation coordinated to a nitrogen atom in one of the aromatic nitrogen-containing aromatic bases to form the metal-containing nucleic acid duplex.

Regarding claim 2, Branton et al teaches the step of reading sequence information from the nucleic acid polymer (column 17, lines 15-18).

Regarding claim 3, Branton et al teaches the detection of presence or absence of nucleic acids by measuring the electrical conductance across the channel as the nucleic acid duplex is translocated through the channel between the hybridization medium and the dissociation medium (Fig. 12B, # 84, column 20, lines 43-47). Branton et al are silent about detecting the presence or absence of the metal cations as the nucleic acid duplex is translocated through the channel.

Regarding claim 5, Branton et al teaches that the channel is formed in a lipid membrane (Fig. 1, and column 6, lines 62-64).

Regarding claim 6, Branton et al teaches that the channel is a pore forming alpha hemolysin protein (Fig. 2, and column 20, lines 65-67).

Regarding claim 7, Branton et al teaches that the hybridization medium and the dissociation medium are electrically conductive aqueous solution (column 16, lines 26-27).

Regarding claim 8, Branton et al teaches that the single stranded poly dA oligonucleotides hybridizes to complementary poly dT oligonucleotides to form a duplex (column 20, line 40), thus teaching first and the second nucleic acid strands are deoxyribonucleic acids and the nitrogen-containing aromatic bases are selected from the group consisting of adenine or thymine.

Regarding claim 9, Branton et al are silent about the metal cation is selected from the group consisting of  $Zn^{2+}$ ,  $Co^{2+}$ , and  $Ni^{2+}$ .

Regarding claim 10, Branton et al teaches that the nitrogen-containing aromatic bases are selected from the group consisting of thymine and guanosine. Branton et al are silent about the metal cations are substituted for imine protons of the nitrogen-containing aromatic bases.

Regarding claim 11, Branton et al teaches that one of the aromatic nitrogen-containing aromatic bases is thymine (column 20, line 39), but are silent about the metal cation is coordinated by the N3 nitrogen atom.

Regarding claim 12, Branton et al silent about at least one of the aromatic nitrogen-containing aromatic bases is guanine, having an N1 nitrogen atom (Fig. 3), but are silent about the metal cation is coordinated by the N1 nitrogen atom.

Regarding claim 13, Branton et al are silent about a process wherein the nucleic acid duplex comprises a base pair mismatch and detecting the presence or absence of divalent metal cations in base pairs of the nucleic acid by measuring the electrical conductance across the channel as the nucleic acid duplex is translocated through the channel. Branton et al are also silent about matching hydrogen bonded base pairs of the metal containing nucleic acid duplex and mismatched base pair does not interchelate a divalent cation.

As described above, Branton et al teaches that the nucleic acids are negatively charged and inherently attracts positively charged metal ions. Branton et al also teaches translocation of different types of nucleic acids under different hybridization conditions varying salt, pH and temperature (column 22, lines 8-15). Branton et al are silent about incorporation of metal ions in a nucleic acid duplex so that metal ion is permitted to enter the duplex for forming a metal containing base pair and if a metal ion is excluded from the duplex a non-metal containing base pair is formed.

However incorporation of metal ions in a nucleic acid duplex was known in the art at the time of the claimed invention was made as taught by Granot et al, who teaches a method comprising incorporation of metal ions in a nucleic acid duplex (Synopsis section) and further teaches that divalent metal cations "stabilize the double helix relative to the single stranded state" (pg. 881, paragraph 2, lines 1-5).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the hybridization medium of Branton et al



with the divalent metal ion media of Granot et al with a reasonable expectation of success.

An artisan would have been motivated to modify the hybridization medium of Branton et al with the expected benefit of having a divalent cation media for stabilizing the nucleic acid duplex as taught by Granot et al (pg. 881, paragraph 2, lines 1-5).

Branton et al and Granot et al are silent about matching hydrogen bonded base pairs of the metal containing nucleic acid duplex and mismatched base pair does not interchelate a divalent cation.

Regarding claims 9-12, Granot et al teaches divalent cation consists of  $Mg^{2+}$  or  $Mn^{2+}$  (pg. 873, Introduction section line 6). Branton et al and Granot et al are silent about the divalent cation being  $Zn^{2+}$ ,  $Co^{2+}$ , and  $Ni^{2+}$  and coordination of metal cation with guanine and thymine bases.

Regarding claim 13, Branton et al and Granot et al are silent about detecting the presence or absence of divalent metal cations in the base pairs of the nucleic acid duplex and mismatched base pair does not interchelate a divalent cation.

However, bond formation between metal ions and nucleic acids and detection of divalent cations were known in the art at the time of the claimed invention was made as taught by Aich et al.

Aich et al teaches a process of forming conductive polymers comprising first and second nucleic acid strands capable of forming a nucleic acid duplex and incorporation of a metal ion in a nucleic acid duplex as the duplex forms in the hybridization medium (Fig. 1, and pg. 5, lines 16-25, pg. 8, lines 9-18). Aich et al further teaches that if a metal

ion is permitted to enter the duplex and a metal containing base pair is formed and if a metal ion is excluded from the duplex a non-metal containing base pair is formed as in B-DNA (Figs. 2 and 4, and pg. 6, lines 14-25).

Aich et al also teaches that the first and the second nucleic acid strands comprise a plurality of nitrogen-containing aromatic bases covalently linked by a backbone, the nitrogen-containing aromatic bases of the first nucleic acid strand being capable of being joined by hydrogen bonding in the hybridization medium to the nitrogen-containing aromatic bases of the second nucleic acid strand so that the nitrogen-containing aromatic bases on the first and the second nucleic acid strands form hydrogen-bonded base pairs in stacked arrangement in the nucleic acid duplex, the hydrogen-bonded base pairs being capable of interchelating the metal cation coordinated to a nitrogen atom in one of the aromatic nitrogen-containing aromatic bases to form the metal-containing nucleic acid duplex (pg. 22, lines 2-13, Aich et al refers to metal containing nucleic acids as M-DNA).

Regarding claims 9 and 10, Aich et al teaches that the divalent metal cations consisting of  $Zn^{2+}$ ,  $Co^{2+}$ , and  $Ni^{2+}$  ions (Aich et al claim 10) and further teaches that the metal cations are substituted for imine protons of the nitrogen-containing aromatic bases, and the nitrogen-containing aromatic bases are selected from the group consisting of thymine and guanosine (Aich et al claim 11).

Regarding claim 11, Aich et al teaches that at least one of the aromatic nitrogen-containing aromatic bases is thymine, having an N3 nitrogen atom, and the divalent metal cation is coordinated by the N3 nitrogen atom (Aich et al claim 12).

Regarding claim 12, Aich et al teaches that at least one of the aromatic nitrogen-containing aromatic bases is thymine, having an N3 nitrogen atom, and the divalent metal cation is coordinated by the N3 nitrogen atom (Aich et al claim 13).

Regarding claim 13, Aich et al teaches a method of detecting mutation comprising nucleic acid duplex having a base pair mismatch further comprising detecting the presence or absence of divalent cation in the base pair of the nucleic acid duplex (Fig. 6, pg. 11, lines 5-21). Aich et al also teaches that the matching hydrogen-bonded base pairs of the metal-containing nucleic acid duplex comprise an interchelated divalent metal cation coordinated to a nitrogen atom in one of the aromatic nitrogen-containing aromatic bases, and wherein a mismatched base pair does not interchelate a divalent cation (Fig. 2 – See the hydrogen bond formation with  $Zn^{2+}$ , Fig. 6- Last left panel -see divalent metal cation chelation with matching base pair, Last right panel-see mismatched base pair does not interchelate with divalent metal ion). Aich et al teaches that for intercalation of divalent cation hydrogen bond formation is necessary between complementary base pairs. In case of mismatched base pair such hydrogen bond formation is dramatically reduced as evidenced by Li et al (PNAS, 1991, 88, 26-30). Li et al teaches that in G:A mismatch pair has only two hydrogen bonds rather than the three hydrogen bonds in the G:C matched pair resulting in duplex instability (Li et al, Fig. 1, Abstract). It is noted that reduction in hydrogen bond formation between mismatched base pair taught by Li et al is used to further support known fact in the art.

Aich et al explicitly teaches that the "conditions for metal ion incorporation into nucleic acid duplex varies from depending on the metal ions and nature of the nucleic

acids and optimization conditions are performed through routine experimentation by varying the parameters (pg. 8, lines 9-18). Thus, combined teachings of Branton et al, Granot et al and Aich et al would provide a process of recording sequence information in a nucleic acid polymer comprising first and second nucleic acids as well as incorporating metal ions as nucleic acid duplex forms in the channel and further recording information as the metal containing duplex translocating through the channel as recited in the instant claim 1.

Aich et al also teaches that formation of metal chelated DNA is sequence specific and allows simultaneous detection of a plurality of sequences yielding abundance of recording information in short time without the necessity of time consuming steps (pg. 11, lines 25-29).

It would have been prima facie obvious to one having the ordinary skill in the art at the time the invention was made to modify the hybridization medium of Branton et al with the metal ion media of Aich et al with a reasonable expectation of success.

An artisan would have been motivated to modify the hybridization medium of Branton et al with the expected benefit of having a sequence specific metal chelation into nucleic acid duplex allowing simultaneous detection of a plurality of sequences yielding abundance of recording information in short time without the necessity of time consuming steps as taught by Aich et al (pg. 11, lines 25-29).

10. Claims 1 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Branton et al (USPN 6,627,067 filed Jun. 22, 2000), Granot et al (Biopolymers, 1982,

21, 873-883) and Aich et al (WO 99/31115, published June 24, 1999) as applied to claim 1 above and further in view of Anazawa et al (USPN 6,136, 543 issued Oct. 24, 2000).

Claim 4 is dependent from claim 1. Teachings of Branton et al, Granot et al and Aich et al regarding claim 1 are described above in section 9.

Regarding claim 4, Branton et al teaches translocation of the nucleic acid duplex through the channel by applying voltage gradient (Fig. 12B and column 20, lines 37-67 and column 21, lines 1-15). Branton et al, Granot et al and Aich et al are silent about nucleic acid duplex attached to magnetic bead. However attachment of nucleic acids to magnetic bead and movement across the pore using magnetic field were known in the art at the time of claimed invention was made as taught by Anazawa et al, who teaches coupling of nucleic acids to a magnetic bead and stretching the DNA duplex using magnetic force in a channel (Fig. 9, magnetic bead # 6, DNA # 7, Abstract and column 8, lines 1-28), thus providing nucleic acid duplex coupled to a magnetic bead and translocation of DNA using magnetic field across the channel.

Thus, as described above, all of the component steps, i.e., coupling of nucleic acid duplex to magnetic bead, modulating the translocation of the DNA duplex in the channel recited in the instantly claimed invention were known in references of Branton et al, Granot et al, Aich et al and Anazawa et al. The only difference is the combination of known method steps of the prior art into a single method to include all the steps, which would be equivalent to a translocation of the nucleic acid duplex through the channel mediated by magnetic field across the channel.

Thus it would have been prima facie obvious to one having ordinary skill in the art to apply the coupling of nucleic acids to magnetic bead and magnetic force taught by Anazawa et al to the translocation of the duplex DNA through the nanopore by the method of Branton et al, Granot et al and Aich et al with the expected benefit of achieving a translocation of DNA using magnetic force.

***Response to remarks from the Applicants***

***Claim Rejections under 35 U.S.C. § 103(a)***

11. Applicant's arguments filed March 9, 2009 with respect to claims 1-3 and 5-13 being unpatentable over Branton et al in view of Aich et al have been considered but are moot in view of the withdrawn rejections and new grounds of rejection set forth in this office action. Applicant's arguments regarding Branton et al and Aich et al as it pertains to their teachings used in this office action are addressed below.

Applicants argue that Branton et al does not contemplate recording information in a nucleic acid polymer (Remarks, pg. 3, paragraph 4). This argument is not persuasive because Branton et al teaches recording the nucleic acid sequence information (column 11, lines 40-46).

Applicants further argue that Branton et al does not provide any discussion or recognition whatsoever of any kind of modulation as duplex forms in a hybridization medium (Remarks, pg. 3, paragraph 4). This argument is not persuasive because as described above in section 9, Branton et al teaches modulating the translocation of single and double stranded nucleic acids using two different voltage gradients (column

20, lines 26-67). Furthermore, Applicants have asserted that Branton et al provide discussion about separation of double stranded DNA and translocation rates of nucleic acid through the channel (Remarks, pg. 3, and paragraph 3). For the above cited reasons arguments are not persuasive.

Applicants further argue that the reference of Aich et al does not contemplate modulating an electrostatic potential across the channel (Remarks pg. 4, paragraph 1). This argument is not persuasive because Applicant's arguments for the nonobviousness are based on attacking the reference of Aich et al individually, where the rejections are based on combinations of Branton et al, Granot et al and Aich et al references.

Furthermore, courts have ruled that arguments by the Applicants of attacking references individually are not persuasive, when the rejections are made with combination of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). As described above in section 9, Branton et al, Granot et al and Aich et al teaches steps 'a' to 'c' as claimed and therefore arguments are not persuasive.

Applicants further reiterate that neither Branton et al nor Aich et al disclose or suggest modulating an electrostatic potential across channel so as to modulate the incorporation of metal ion in a nucleic acid duplex as the duplex forms (Remarks, pg. 5, paragraphs 2 and 3). This argument is not persuasive because Applicants have asserted that Branton et al teaches voltage gradient to translocate nucleic acid through channel (Remarks, pg. 3, paragraph 3, pg. 5, paragraph 2) and as described above in section 9, Granot et al teaches the incorporation of metal ions in a nucleic acid for

stabilizing the duplex. Also, voltage gradient is the preferred mode of generating electrostatic potential across the channel as defined in the instant specification (USPGPUB, paragraph 0037). Since Branton et al and Granot et al teach metal ion incorporation in a nucleic acid as duplex forms in the channel arguments are not persuasive.

Applicants further reiterate that variations in voltage gradient disclosed by Branton et al do not appear to take place as a duplex forms (Remarks, pg. 5, paragraph 4, pg. 6, and paragraph 1). This argument is not persuasive because Branton et al explicitly teaches that only under higher voltage gradient duplex is in the channel (column 20, lines 37-52) and Granot et al teaches nucleic acid incorporation of metal ion in a nucleic acid for stabilizing the nucleic acid duplex. Furthermore, arguments of counsel are not found persuasive in the absence of factual showing. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long-felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant.

In the instant case, Applicants have asserted that Branton et al teach duplex formation by voltage gradient. Granot et al teaches stabilizing the duplex by incorporating metal ions in a nucleic acid and therefore arguments are not persuasive.



Applicants further reiterate that there are numerous significant differences between Aich and subject matter of claim 1 (Remarks, pg. 6, paragraph 2). These arguments are not persuasive for the same reasons as described above.

Applicants further make the case for non-obviousness reiterating the same arguments with respect to teachings of Branton et al and Aich et al (Remarks, pgs. 6-8). These arguments are not persuasive for the same reasons as described above and in view of new rejection as set forth in section 9 and 10.

Applicant's argument with respect to claim 4 being unpatentable over Branton et al, Aich et al and Anazawa et al are not persuasive (Remarks, pgs. 8 and 9) because the arguments are directed towards modulating electrostatic potential across the channel to modulate the incorporation of a metal ion in a nucleic acid duplex. Furthermore, Applicant has not traversed the teachings, suggestions or motivation of Anazawa et al. As described above in section 10, Branton et al, Granot et al, Aich et al and Anazawa et al teaches steps recited in claim 4, arguments are not persuasive.

### ***Conclusion***

12. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Narayan K. Bhat whose telephone number is (571)-272-5540. The examiner can normally be reached on 8.30 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram R. Shukla can be reached on (571)-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Narayan K. Bhat/

Examiner, Art Unit 1634

/Ram R. Shukla/

Supervisory Patent Examiner, Art Unit 1634